

Amendments to the Claims

This listing of claims replaces all prior versions and listings of claims in the application. The amendments made herein are made without prejudice or disclaimer.

Listing of Claims:

1-37. (Cancel)

38. (New) An insulin derivative comprising an insulin molecule and a reactive group for covalently bonding a blood protein, the reactive group being a maleimido-containing group, wherein the reactive group is coupled to an available amino group of the insulin molecule selected from the α -amino groups of the N-terminus amino acids of chains A and B and the ϵ -amino group of Lys B29.

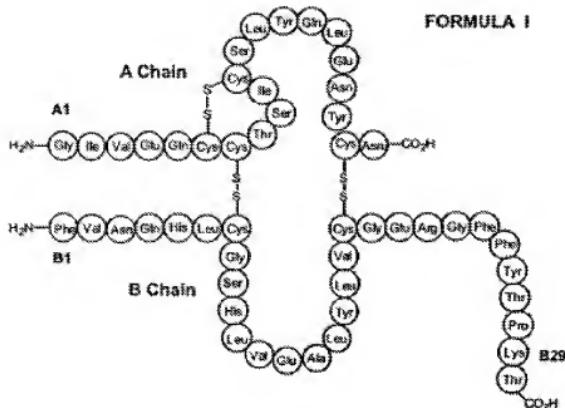
39. (New) The insulin derivative of claim 38, wherein the available amino group is the ϵ -amino group of Lys B29.

40. (New) The insulin derivative of claim 38, wherein the available amino group is the α -amino group of Gly A1.

41. (New) The insulin derivative of claim 38, wherein the available amino group is the α -amino group of Phe B1.

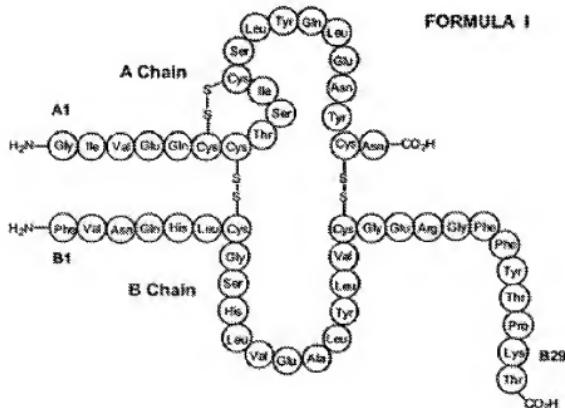
42. (New) The insulin derivative of claim 38, wherein the insulin molecule is selected from the group consisting of insulin glargine, insulin detemir, insulin lispro, insulin aspart and insulin glulisine.

43. (New) The insulin derivative of claim 38, wherein the insulin molecule is of formula I:

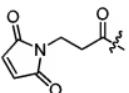


and the reactive group is coupled to an amino acid of the insulin molecule at a position selected from the positions Gly A1, Phe B1 and Lys B29.

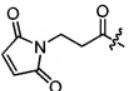
44. (New) The insulin derivative of claim 41, wherein the insulin molecule is of formula I:



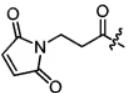
45. (New) The insulin derivative of claim 38, wherein the reactive group coupled to the available amino group of the insulin molecule is:



46. (New) The insulin derivative of claim 41, wherein the reactive group coupled to the available amino group of the insulin molecule is:



47. (New) The insulin derivative of claim 44, wherein the reactive group coupled to the available amino group of the insulin molecule is:



48. (New) The insulin derivative of claim 38, wherein the reactive group is coupled to the available amino group of the insulin molecule via a linker.

49. (New) The insulin derivative of claim 41, wherein the reactive group is coupled to the available amino group of the insulin molecule via a linker.

50. (New) The insulin derivative of claim 46, wherein the reactive group is coupled to the available amino group of the insulin molecule via a linker.

51. (New) The insulin derivative of claim 47, wherein the reactive group is coupled to the available amino group of the insulin molecule via a linker.

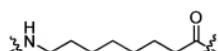
52. (New) The insulin derivative of claim 48, wherein the reactive group is coupled to the available amino group of the insulin molecule by reacting a linker with the reactive group and the available amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2\text{-}(\text{CH}_2)_n\text{-COOH}$ where n is an integer between 1 and 20.

53. (New) The insulin derivative of claim 49, wherein the reactive group is coupled to the available amino group of the insulin molecule by reacting a linker with the reactive group and the available amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2\text{-}(\text{CH}_2)_n\text{-COOH}$ where n is an integer between 1 and 20.

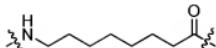
54. (New) The insulin derivative of claim 50, wherein the reactive group is coupled to the available amino group of the insulin molecule by reacting a linker with the reactive group and the available amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2\text{-}(\text{CH}_2)_n\text{-COOH}$ where n is an integer between 1 and 20.

55. (New) The insulin derivative of claim 51, wherein the reactive group is coupled to the available amino group of the insulin molecule by reacting a linker with the reactive group and the available amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2\text{-}(\text{CH}_2)_n\text{-COOH}$ where n is an integer between 1 and 20.

56. (New) The insulin derivative of claim 48, wherein the linker is:



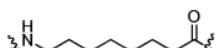
57. (New) The insulin derivative of claim 49, wherein the linker is:



58. (New) The insulin derivative of claim 50, wherein the linker is:



59. (New) The insulin derivative of claim 51, wherein the linker is:



60. (New) The insulin derivative of claim 43, wherein the insulin molecule is coupled at the terminal Gly of A1 with 3-maleimidopropanamide, and wherein the α -amino group of Gly is the amide nitrogen of the 3-maleimidopropanamide.

61. (New) The insulin derivative of claim 44, wherein the insulin molecule is coupled at the terminal Phe of B1 with 3-maleimidopropanamide, and wherein the α -amino group of Phe is the amide nitrogen of the 3-maleimidopropanamide.

62. (New) The insulin derivative of claim 44, wherein the insulin molecule is coupled at the terminal Phe of B1 with 8-N-(3-maleimidopropylcarbonyl)aminoctanamide, and wherein the α -amino group of Phe is the amide nitrogen of the octanamide of 8-N-(3-maleimidopropylcarbonyl)aminoctanamide.

63. (New) The insulin derivative of claim 43, wherein the insulin molecule is coupled at the B29 Lys with 3-maleimidopropanamide and wherein the ϵ -amino group of Lys is the amide nitrogen of the 3-maleimidopropanamide.

64. (New) The insulin derivative of claim 38, wherein the blood protein is albumin.

65. (New) The insulin derivative of claim 64, wherein the albumin is recombinant albumin.

66. (New) An insulin conjugate comprising an insulin molecule, a reactive group and a blood protein, the reactive group being a maleimido-containing group, wherein the reactive group is coupled to an available amino group of the insulin molecule selected from the α -amino groups of the N-terminus amino acids of chains A and B and the ϵ -amino group of Lys B29, and wherein the reactive group is covalently bonded to the blood protein.

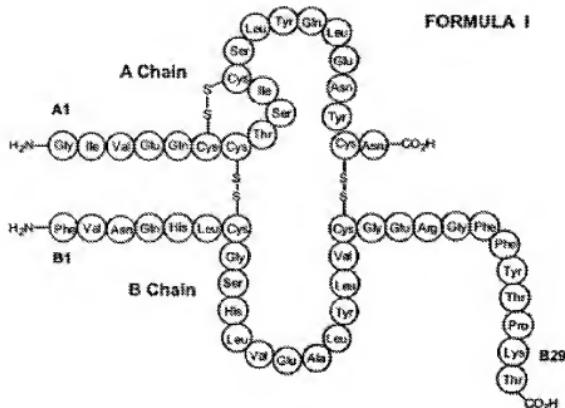
67. (New) The insulin conjugate of claim 66, wherein the available amino group is the ϵ -amino group of Lys B29.

68. (New) The insulin conjugate of claim 66, wherein the available amino group is the α -amino group of Gly A1.

69. (New) The insulin conjugate of claim 66, wherein the available amino group is the α -amino group of Phe B1.

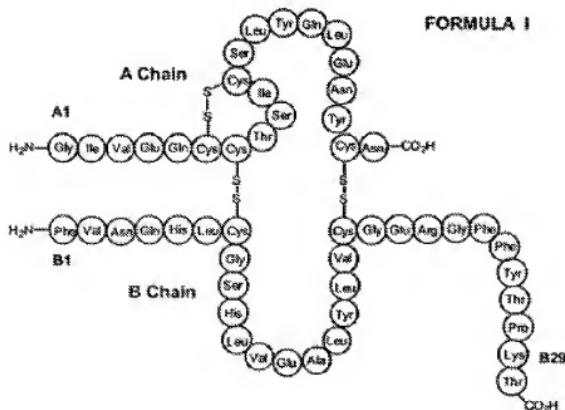
70. (New) The insulin conjugate of claim 66, wherein the insulin molecule is selected from the group consisting of insulin glargine, insulin detemir, insulin lispro, insulin aspart and insulin glulisine.

71. (New) The insulin conjugate of claim 66, wherein the insulin molecule is of formula I:

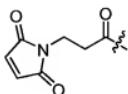


and the reactive group is coupled to an amino acid of the insulin molecule at a position selected from the positions Gly A1, Phe B1 and Lys B29.

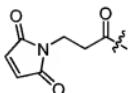
72. (New) The insulin conjugate of claim 69, wherein the insulin molecule is of formula I:



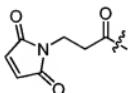
73. (New) The insulin conjugate of claim 66, wherein the reactive group coupled to the available amino group of the insulin molecule is:



74. (New) The insulin conjugate of claim 69, wherein the reactive group coupled to the available amino group of the insulin molecule is:



75. (New) The insulin conjugate of claim 72, wherein the reactive group coupled to the available amino group of the insulin molecule is:



76. (New) The insulin conjugate of claim 66, wherein the reactive group is coupled to the available amino group of the insulin molecule via a linker.

77. (New) The insulin conjugate of claim 69, wherein the reactive group is coupled to the available amino group of the insulin molecule via a linker.

78. (New) The insulin conjugate of claim 74, wherein the reactive group is coupled to the available amino group of the insulin molecule via a linker.

79. (New) The insulin conjugate of claim 75, wherein the reactive group is coupled to the available amino group of the insulin molecule via a linker.

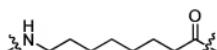
80. (New) The insulin conjugate of claim 76, wherein the reactive group is coupled to the available amino group of the insulin molecule by reacting a linker with the reactive group and the available amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2\text{-(CH}_2\text{)}_n\text{-COOH}$ where n is an integer between 1 and 20.

81. (New) The insulin conjugate of claim 77, wherein the reactive group is coupled to the available amino group of the insulin molecule by reacting a linker with the reactive group and the available amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2\text{-(CH}_2\text{)}_n\text{-COOH}$ where n is an integer between 1 and 20.

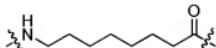
82. (New) The insulin conjugate of claim 78, wherein the reactive group is coupled to the available amino group of the insulin molecule by reacting a linker with the reactive group and the available amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2\text{-(CH}_2\text{)}_n\text{-COOH}$ where n is an integer between 1 and 20.

83. (New) The insulin conjugate of claim 79, wherein the reactive group is coupled to the available amino group of the insulin molecule by reacting a linker with the reactive group and the available amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and $\text{NH}_2\text{-(CH}_2\text{)}_n\text{-COOH}$ where n is an integer between 1 and 20.

84. (New) The insulin conjugate of claim 76, wherein the linker is:



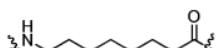
85. (New) The insulin conjugate of claim 77, wherein the linker is:



86. (New) The insulin conjugate of claim 78, wherein the linker is:



87. (New) The insulin conjugate of claim 79, wherein the linker is:



88. (New) The insulin conjugate of claim 71, wherein the insulin molecule is coupled at the terminal Gly of A1 with 3-maleimidopropanamide, and wherein the α -amino group of Gly is the amide nitrogen of the 3-maleimidopropanamide.

89. (New) The insulin conjugate of claim 72, wherein the insulin molecule is coupled at the terminal Phe of B1 with 3-maleimidopropanamide, and wherein the α -amino group of Phe is the amide nitrogen of the 3-maleimidopropanamide.

90. (New) The insulin conjugate of claim 72, wherein the insulin molecule is coupled at the terminal Phe of B1 with 8-N-(3-maleimidopropylcarbonyl)aminoctanamide, and wherein the α -amino group of Phe is the amide nitrogen of the octanamide of 8-N-(3-maleimidopropylcarbonyl)aminoctanamide.

91. (New) The insulin conjugate of claim 71, wherein the insulin molecule is coupled at the B29 Lys with 3-maleimidopropanamide and wherein the ϵ -amino group of Lys is the amide nitrogen of the 3-maleimidopropanamide.

92. (New) The insulin conjugate of claim 66, wherein the blood protein is albumin.

93. (New) The insulin conjugate of claim 92, wherein the albumin is recombinant albumin.

94. (New) The insulin conjugate of claim 69, wherein the blood protein is albumin.
95. (New) The insulin conjugate of claim 94, wherein the albumin is recombinant albumin.
96. (New) The insulin conjugate of claim 72, wherein the blood protein is albumin.
97. (New) The insulin conjugate of claim 96, wherein the albumin is recombinant albumin.
98. (New) The insulin conjugate of claim 73, wherein the blood protein is albumin.
99. (New) The insulin conjugate of claim 98, wherein the albumin is recombinant albumin.
100. (New) The insulin conjugate of claim 74, wherein the blood protein is albumin.
101. (New) The insulin conjugate of claim 100, wherein the albumin is recombinant albumin.
102. (New) The insulin conjugate of claim 75, wherein the blood protein is albumin.
103. (New) The insulin conjugate of claim 102, wherein the albumin is recombinant albumin.
104. (New) The insulin conjugate of claim 84, wherein the blood protein is albumin.
105. (New) The insulin conjugate of claim 104, wherein the albumin is recombinant albumin.
106. (New) The insulin conjugate of claim 85, wherein the blood protein is albumin.
107. (New) The insulin conjugate of claim 106, wherein the albumin is recombinant albumin.

108. (New) The insulin conjugate of claim 86, wherein the blood protein is albumin.
109. (New) The insulin conjugate of claim 108, wherein the albumin is recombinant albumin.
110. (New) The insulin conjugate of claim 87, wherein the blood protein is albumin.
111. (New) The insulin conjugate of claim 110, wherein the albumin is recombinant albumin.
112. (New) The insulin conjugate of claim 89, wherein the blood protein is albumin.
113. (New) The insulin conjugate of claim 112, wherein the albumin is recombinant albumin.
114. (New) The insulin conjugate of claim 90, wherein the blood protein is albumin.
115. (New) The insulin conjugate of claim 114, wherein the albumin is recombinant albumin.
116. (New) A pharmaceutical composition comprising an insulin derivative of claim 38 and a pharmaceutically acceptable carrier.
117. (New) A pharmaceutically acceptable carrier comprising an insulin conjugate of claim 66 and a pharmaceutically acceptable carrier.
118. (New) A method of treating a glycaemic-related disease in a subject, comprising:
administering to the subject an insulin derivative of claim 38, to thereby treat the
glycaemic related disorder.
119. (New) The method of claim 118, wherein the glycaemic-related disease or disorder is selected from the group consisting of diabetes, diabetes of type I, diabetes of type II and gestational diabetes.

120. (New) The method of claim 118, wherein the glycaemic-related disease or disorder is selected from the group consisting of diabetes of type I and diabetes of type II.

121. (New) A method of treating a glycaemic-related disease in a subject, comprising:
administering to the subject an insulin conjugate of claim 66, to thereby treat the glycaemic related disorder.

122. (New) The method of claim 121, wherein the glycaemic-related disease or disorder is selected from the group consisting of diabetes, diabetes of type I, diabetes of type II and gestational diabetes.

123. (New) The method of claim 121, wherein the glycaemic-related disease or disorder is selected from the group consisting of diabetes of type I and diabetes of type II.

124. (New) A method of making the conjugate of claim 66 *in vivo* in a subject, the method comprising administering to a subject an insulin derivative of claim 38, wherein a covalent bond between the reactive group of the insulin derivative and the blood protein is formed in the subject.

125. (New) A method of forming the conjugate of claim 66 *ex vivo*, the method comprising combining the insulin derivative of claim 38 with a blood protein, wherein a covalent bond forms between the reactive group of the insulin derivative and the blood protein.

126. (New) A method of treating cystic fibrosis in a subject, comprising:
administering to the subject an insulin derivative of claim 38 or an insulin conjugate of claim 66, to thereby treat the cystic fibrosis.

127. (New) A method of treating polycystic ovary syndrome in a subject, comprising:
administering to the subject an insulin derivative of claim 38 or an insulin conjugate of claim 66, to thereby treat the polycystic ovary syndrome.

128. (New) A method of treating pancreatitis in a subject, comprising:
administering to the subject an insulin derivative of claim 38 or an insulin conjugate of
claim 66, to thereby treat the pancreatitis.

129. (New) A method of treating a pancreatic related disorder in a subject, comprising:
administering to the subject an insulin derivative of claim 38 or an insulin conjugate of
claim 66, to thereby treat the pancreatic related disorder.

130. (New) A method of treating a wound in a subject, comprising:
administering to the would an insulin derivative of claim 38 or an insulin conjugate of
claim 66, to thereby treat the wound.

131. (New) The insulin derivative of claim 41, wherein the N-terminus amino acid of the A
chain and the LysB29 of the insulin molecule is Boc protected.